REMARKS

Claims 1-10 and 12 are pending after entry of the amendments set forth herein. Claims 13-16 are canceled without prejudice. Claims 1, 4, 8, 9 and 12 are amended. Support for the amending language "percutaneous injection" may be found in the specification at paragraph 38. Support for the amending language "increasing blood flow" with respect to cardiovascular disease may be found in the specification at paragraph 58. Claims 4 and 9 have been rewritten in independent form; and the dependency of Claim 12 has been amended in view of the cancellation of Claim 11. No new matter is added. Reconsideration is requested.

Rejections of canceled claims are made moot and will not be further considered.

REJECTIONS UNDER §112, ¶1

Claims 8-13 and 15-16 have been rejected under 35 U.S.C. 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants respectfully submit that the presently claimed invention is enabled by the specification and meets the requirements of 35 U.S.C. 112, first paragraph. The Office Action states that the specification, while being enabling for decreasing pain which accompanies cardiovascular conditions, does not reasonably provide enablement for treatment of the cardiovascular conditions themselves".

Applicants respectfully disagree with this assessment, and request a review of the present specification with respect to Example 3 (paragraph 76) and Example 4 (paragraph 77). The examples found that for a patient with an ischemic foot, or in 6 patients with peripheral vascular disease, there was an improvement in function, including improved blood flow, when the patients were treated with a sympathetic block. Applicants note that Claim 8 has been amended to recite specific cardiovascular conditions; and Claim 9 has been rewritten in independent form to specifically claim the treatment of peripheral vascular disease.

As discussed in the specification at paragraph 58, the inventive methods of toxin mediated sympathetic block find use in the treatment of cardiovascular conditions that benefit from decreased sympathetic activation. Sympathetic activation increases myocardial work and oxygen demand creating a mismatch between available supply and demand as the underlying physiology behind ischemic cardiac disease. Interruption of sympathetic stimulation does not just reduce the associated pain but reverses the underlying pathophysiology. Additionally,

sympathetic activation causes vasoconstriction in regions such as the renal and splanchnic circulations, which redistributes cardiac output to the exercising muscles. Interruption of sympathetic stimulation of the cardiovascular system can provide for increased blood flow to targeted tissues, as observed by Applicants in the treatment of patients.

In view of the above amendments and remarks, Applicants respectfully submit that the presently claimed invention is enabled by the specification. Withdrawal of the rejection is requested.

REJECTIONS UNDER §103(A)

Claims 1-3 and 5-6 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002. Autonomic Neuroscience 102:8-12; cited on IDS filed 22 February 2007). Applicants respectfully submit that the present claims are not made obvious by the cited art. Applicants note that the claims have been amended to include the limitation that the botulinum toxin is percutaneously injected at the site of a sympathetic ganglion. In addition, Claim 4 has been rewritten in independent form.

The primary reference, Kim et al. is asserted to teach that: "sympathetically mediated chronic pain is mediated by the sympathetic ganglion (see p. 8 first paragraph). The reference teaches administration of botulinum toxin type A, recited in claims 1 and 2. The reference teaches that the dose used was 2-10 units per kilogram of body weight, administered to rabbits, which is within the range recited in claim 3, given that rabbits weigh less than 30 kg. The reference teaches administration to the superior cervical ganglion as recited in claim 5-6. However Kim does not teach administration to humans, as recited in claim 1." It is further asserted that the modification to treat humans would be obvious "as the rabbits used by Kim are a model of human physiology".

Applicants wish to first review the data provided by Kim *et al.* The reference is directed at methods of selectively killing nerves, as stated in the abstract, "In this study, after the administration of BTA into the superior cervical ganglion (SCG) in rabbits, the possible clinical use of BTA as a neurolytic agent was evaluated." The methods involved surgically opening the neck region, and perfusing the superior cervical ganglion with BTA. It was then determined whether this procedure induced miosis, *i.e.* constriction of the pupil of the eye. The effect of the procedure was compared to animals where the ganglion was removed completely.

The authors found that all of the rabbits that had been given 10 U of BTA died. "A 30% responsiveness was seen in the 2 U group (3/10), and 35% responsiveness in the 5 U group"

and "significant variation was found in terms of the onset time and duration of miosis." The presence or absence of papillary constriction (miosis) was determined by review of an investigator – no measurements were taken to provide quantitative data. Indeed, the authors note "the lack of a close agreement between the BTA injection and resultant occurrence of miosis".

Oddly, while it was found that while "both of the rabbits in the ganglionectomy group showed miosis over the 6-week period", "rabbits which underwent sympathetic ganglionectomy as positive control for miosis, showed reversal of miosis 6 weeks later." The reference fails to explain how the rabbits in which the ganglion had been surgically removed were able to regain function.

Applicants respectfully submit that Kim *et al.* fail to demonstrate a role for BTA in blocking sympathetically maintained pain; and fail to make obvious methods of treating a human by the methods of the present invention.

As noted above, Kim *et al.* demonstrate that destruction of certain nerve ganglia provide for a reversible miosis in rabbits. They also describe an admittedly lack of close agreement between their BTA procedure and miosis. In view of this lack of close association between the treatment, and the lack of rigor in the assessment of results (for example the lack of quantitative data); Applicants respectfully submit that the cited reference fails to teach even an association of miosis with their procedure.

Further, even assuming, *arguendo*, that the cited art taught a connection between miosis and the administration of BTA, a correlation is not made between miosis and relief of sympathetic pain. Indeed, even the authors of study never make a claim that there is a direct correlation between miosis and pain relief. And since the onset of miosis is reversible even when the sympathetic ganglion is surgically removed, one of skill in the art should rightly doubt that the effect can be due to a direct effect on the sympathetic nerves, as the ganglion cannot be regrown to restore the lost function. In other animal models, it is noted that "because different neurotransmitters are involved in pupil and pain mechanisms of antidepressant drugs, it is difficult to evaluate the analgesic response with the pupil diameter." (Onal *et al.* Gen Pharmacol. 1999 Jul;33(1):83-9).

Even if one were able to make the assumption that Kim *et al.* taught a correlation between the small number of animals showing miosis, and pain relief, one of skill in the art

would not readily extrapolate such findings to the treatment of humans. The methods of the present invention relate to treatment of neuropathic pain.

For such neuropathic pain, animal models are not necessarily predictive of human behavior. As explained in the attached reference by Campbell and Meyer:

> Animal models of neuropathic pain in some cases have been inconsistent with human models. Allodynia in painful diabetic neuropathy in humans is infrequent yet appears to be robust in rat models. NK1 antagonists appeared to have promise for treatments of pain based on animal models yet to date have not proven useful in patients. Vierck (2006) argues that "reflex" measures of pain in animal neuropathic models are intrinsically flawed and are neither sensitive nor specific predictors of drug efficacy in man. For example, he points out that the paw withdrawal threshold method tests motor neuron response rather than simply providing a measure of pain. Moreover, he indicates that rostral signaling pathways may be ignored when one merely measures the paw-withdrawal threshold.

Thus one of skill in the art has reason to doubt the extrapolation of animal models such as those shown by Kim *et al.*, with the treatment of human neuropathic pain.

Applicants further note that the methods of Kim *et al.*, which use surgical dissection and perfusion of the nerve, are directed at neurolytic techniques. The present application notes that "When a neurolytic agent is used, axonal damage results leading to unpredictable regrowth of the nerves. Additionally, significant scarring in the area occurs, which limits the ability to perform repeated neurolytic blocks. Finally, spread of the neurolytic solution can occur to other structures leading to significant neurological or vascular injury."

In contrast, the methods of the present invention, which rely on percutaneous injection of toxin, provide for "a more complete, and longer acting sympathetic block, which does not permanently damage the nerve" (specification, paragraph 17).

In view of the above amendments and remarks, Applicants respectfully submit that the invention of Claims 1-3 and 5-6 are not made obvious by the cited art. Withdrawal of the rejection is requested.

Claims 1-3 and 5-7 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) as applied to claims 1-3 and 5-6 above, and further in view of Erickson (1993. Radiology 188:707-709).

Applicants respectfully submit that Kim et al. fails to teach the presently claimed invention, as described above. The secondary art fails to remedy the deficiencies of the primary reference. Erickson teaches administration of local anesthetic as a sympathetic block, but fails to suggest the use of botulinum toxin in treating sympathetically maintained pain. The active

agents utilized by Erickson et al. include Bupivacaine and Lidocaine, which bind to the intracellular portion of sodium channels and blocks sodium influx into nerve cells, preventing depolarization. The effect is primarily on pain transmitting neurons.

In contrast, the methods of the present invention provide for a selective block of acetylcholine release from the targeted sympathetic ganglion, thereby preventing the maintenance of pain. The mechanism of action is different, and the nerves primarily affected by the therapeutic agent are different.

Applicants respectfully submit that the cited combination of art does not teach or suggest the presently claimed invention. Withdrawal of the rejection is requested.

Claims 1-6 have rejected under 35 U.S.C. 103(a) as being unpatentable over Kim (2002) as applied to claims 1-3 and 5-6 above, and further in view of Brushey (U.S. Patent Application Publication 2001/0056275, published 27 December 2001).

Applicants respectfully submit that Kim *et al.* fails to teach the presently claimed invention, as described above. The secondary art fails to remedy the deficiencies of the primary reference. As cited by the Examiner, Brushey *et al.* teach that

> [0004] Peripheral pain management procedures are continuous peripheral nerve blocks which can be categorized into two types depending on the area of the body where the block is introduced. In upper extremity blocks, the majority of the continuous peripheral nerve blocks performed are in the brachial plexus, i.e., the shoulder and neck regions. Such nerve blocks in the area of the brachial plexus include: interscalene block, supraclavicular block and axillary block.
> [0005] In lower extremity blocks, the majority of the continuous nerve blocks performed are in the lumbar plexus and the celiac plexus, i.e., the hips and waist areas. Nerve blocks performed in the region of the lumbar plexus are: sciatic block, femoral block, lateral femoral block, obturator block, popliteal block, ankle block and lumbar sympathetic block. Nerve blocks performed in the area of the celiac plexus include: the celiac plexus block, which blocks the splanchnic nerve bundle.

Thus, the cited art teaches certain locations for peripheral pain management, but fail to teach or suggest the use of botulinum toxin in treating sympathetically maintained pain.

Applicants respectfully submit that the cited combination of art does not teach or suggest the presently claimed invention. Withdrawal of the rejection is requested.

Claims 1-3, 5-6, and 8-12 have rejected under 35 U.S.C. 103(a) as being unpatentable over Hernard (1982. Arch Mal Coeur 75(11):1317-1320, cited on IDS filed 22 February 2007) in view of Kim (2002).

Applicants respectfully submit that Kim *et al.* fails to teach the presently claimed invention, as described above. The secondary art fails to remedy the deficiencies of the primary reference. Henard *et al.* relates to the use of surgical methods to treat coronary vasospasm, and does not provide teachings relevant to the treatment of pain.

With respect to Claims 8-12, Henard *et al.* fail to teach the novel use of botulinum toxin to decrease sympathetic activation for the treatment of cardiovascular conditions such as peripheral vascular disease. Such methods are also not taught or suggested by Kim *et al.*

Applicants respectfully submit that the cited combination of art does not teach or suggest the presently claimed invention. Withdrawal of the rejection is requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number STAN-332.

Respectfully submitted,
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Date: March 14, 2008

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1: Anesthesiology. 1996 Oct;85(4):748-54.

Sympathetic nervous system does not mediate reflex pupillary dilation during desflurane anesthesia.

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BACKGROUND: Pupil size is determined by an interaction between the sympathetic and parasympathetic divisions of the autonomic nervous system. Noxious stimulation dilates the pupil in both unanesthetized and anesthetized humans. In the absence of anesthesia, dilation is primarily mediated by the sympathetic nervous system. In contrast, pupillary dilation in cats given barbiturate or cloralose anesthesia is mediated solely by inhibition of the midbrain parasympathetic nucleus. The mechanism by which noxious stimuli dilate pupils during anesthesia in humans remains unknown. Accordingly, the authors tested the hypothesis that the pupillary dilation in response to noxious stimulation during desflurane anesthesia is primarily a parasympathetic reflex. METHODS: In six volunteers, the alpha-I adrenergic receptors of the iris musculature were blocked by unilateral administration of topical dapiprazole; six other volunteers were given unilateral topical tropicamide to block the muscarinic receptors in the iris. Desflurane anesthesia was subsequently induced in all volunteers. Sympathetic nervous system activation, with reflex dilation of the pupil, was produced by noxious electrical stimulation during 4% and 8% end-tidal desflurane, and by a rapid 4%-to-8% step-up in the desflurane concentration. Pupil diameter and the change in pupil size induced by a light stimulus (light reflex amplitude) were measured with infrared pupillometry. RESULTS: Dapiprazole drops produced a Horner's miosis, but pupils were equally small after induction of anesthesia. Pupillary dilation after noxious stimulation and desflurane step-up was identical in the unblocked and dapiprazole-blocked pupils. After tropicamide administration, the pupil was dilated and the light reflex was completely inhibited. Noxious stimulation nonetheless produced a slight additional dilation. CONCLUSIONS: During desflurane anesthesia, pupillary dilation in response to noxious stimulation or desflurane step-up is not mediated by the sympathetic nervous system (as it is in unanesthetized persons). Although inhibition of the pupillo-constrictor nucleus may be the cause of this dilation, the mechanism remains unknown.

PMID: 8873544 [PubMed - indexed for MEDLINE]

1: Gen Pharmacol. 1999 Jul;33(1):83-9.

The relationship between pupil diameter and pain by the administration of morphine and antidepressant drugs in mice.

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Because the pain sensation is subjective, it is difficult to evaluate the responses to analgesic drugs. Some analgesics that affect the central nervous system are known to change the pupil diameter. The pupil diameter is a more objective criterion that shows the drug effect. We studied the relation between the pupil diameter and analgesia responses to morphine and antidepressants by using the selective micro-receptor agonist morphine (2 and 4 mg/kg), the noradrenaline reuptake inhibitor desipramine (7.5 and 10 mg/kg), the mixed serotonergic and noradrenergic uptake inhibitor and cholinergic receptor antagonist amitriptyline (2.5 and 5 mg/kg), and the selective serotonin reuptake inhibitor sertraline (2.5 and 5 mg/kg) in mice. Both monocular microscopy to assess pupil measurement and the hot-plate test to assess nociceptive thresholds were used in the same animals. We found that morphine played an important role in both mydriasis and analgesia, whereas amitriptyline and desipramine had a greater effect on pupil response than on nociception. Sertraline produced antinociception without causing a change in pupil diameter. As a result, although the pupil response is an important criterion in evaluating the analgesic effect of morphine, it is not possible to put forward the same criterion for the antidepressant drugs. Because different neurotransmitters are involved in pupil and pain mechanisms of antidepressant drugs, it is difficult to evaluate the analgesic response with the pupil diameter.

PMID: 10428020 [PubMed - indexed for MEDLINE]